

AMENDMENTS TO THE SPECIFICATION

Please replace the “BRIEF DESCRIPTION OF THE DRAWINGS” at page 5, line 27 – page 6, line 23, with the following:

Figure 1A shows the reconstruction of a human B cell line (CD19⁺ cells) in recipient mice. a, b, c, and d represent the flow cytometry of cells collected from the bone marrow (BM); the spleen; the peripheral blood (PB); and the lymph nodes (LN), respectively.

Figure 1B shows the expression of various types of human immunoglobulins in recipient mice. Panels in the first row (e), panels in the second row (f), panels in the third row (g), and panels in the fourth row (h) represent the results obtained by staining the hematopoietic cells derived from the BM, the spleen, the PB, and the LN with FITC-binding IgM (at the first column), IgD (at the second column), IgG (at the third column) and IgA (at the fourth column), and PE-binding CD19 antibody, respectively. The numerical value in each panel represents the ratio (%) of cells expressing each class of immunoglobulin in the CD19⁺ cells.

Figure 2 shows the results of ELISA performed on OVA-specific IgM. Panel a represents the results of IgM, and panel b represents the results of IgG. The bars in the figure represent blood plasma, culture supernatant, negative control 1 (human serum), and negative control 2 (a tenth part of the serum as negative control 1), from the left.

Figure 3 shows the reconstruction of a human T cell line in the bone marrow, spleen, and peripheral blood of recipient mice. The panels in Figures 3a to 3c represent the analysis results of BM (a), those of spleen (b), and those of PB (c), respectively. The panels in Figures 3d and 3e represent the analysis results of BM (d) and those of thymus gland (e), respectively.

Figure 4 shows the results obtained by the FISH analysis and immunohistological analysis of lymphoid tissues. Figure 4a shows human cells identified as green signals (human X

chromosomes). Figure 4c shows several spleen cells derived from the recipient mice stained with mouse anti-human CD3 (red). Figure 4b is a view obtained by overlaying panel a on panel c. The blue-stained portion represents a nucleus. Figures 4d and 4e show the results obtained by immunohistological staining of spleen tissues collected from mice. Figure 4f shows a portion of the spleen stained with anti-human CD3 (red). Figure 4g represents the presence of human APCs.

Figure 5 shows the identification of human erythrocyte compositions in the bone marrow (BM) of NOD/SCID/IL2rg-null mice. A: human GPA⁺ erythrocytes and human CD41⁺ megakaryocytes; B: CD33⁺ spinal cord cells; C: CD19⁺B cells; D: CD3⁺T cells; E: human mature erythrocytes; F: human mature thrombocytes.

Figure 6 shows the generation of human B cells in the BM and spleen of NOD/SCID/IL2rg-null mice. A: CD19⁺CD20^{hi} mature B cells; B: CD10⁺CD19⁺ immature B cells; C: CD34⁺CD19⁺pro-B cells; D: CD19⁺CD20^{hi} mature B cells; E: CD10⁺CD19⁺ immature B cells; F: CD34⁺CD19⁺pro-B cells.

Figure 7 shows the expression of human immunoglobulins in CD19⁺ B lineage cells derived from the BM, peripheral blood (PB), and spleen, 3 months after the transplantation. The number in each dot plot represents the ratio (%) of cells, which exhibited positive to both the antibody for each marker representing the origin of the cells and the antibody belonging to each immunoglobulin class. A-D: BM; E-H: PB; I-L: spleen.

Figure 8 shows the generation of human T cells in NOD/SCID/IL2rg-null mice. A: thymus gland; B: spleen; C: the T cells in the thymus gland stained with an anti-human CD4 antibody; D: the T cells in the thymus gland stained with an anti-human CD8 antibody; E: a view obtained by overlaying Figure 8C on Figure 8D; F: the spleen stained with an anti-human CD4 antibody (green) and an anti-human CD8 antibody (red).

Figure 9 shows the presence of human dendritic cells in the spleen of NOD/SCID/IL2rg-null mice. Figure 9A shows the presence of HLA⁺DR⁺CD11c⁺ cells in the spleen by flow cytometry. Figure 9B is a view showing that it was found as a result of immunostaining with an anti-human CD11c antibody that human dendritic cells have estimated morphologic characteristics. The presence of human dendritic cells indicates that structures are formed with human CD19⁺ cells and CD3⁺ cells in the spleen of the recipient (Figures 9C and 9D).

Figure 10 shows the generation of mucosal immunity in the intestine of NOD/SCID/IL2rg-null mice. Figures 10A and 10B show nuclei stained with DAPI. These figures also show that human mucosal immunity is present in the intestine sample of the recipient mice, as a result of immunostaining with an anti-human CD3 antibody (A, green) and with an anti-human IgA antibody (B, red). Figure 10C is a view showing the contours of villus obtained by DIC imaging. Figure 10D is a view obtained by overlaying A, B, and C. Figure 10E shows a modal structure observed below the chorion of ileum of an engrafted mouse. Figure 10F shows the Peyer's patch-like structure stained with an anti-human IgA antibody (red) and an anti-human CD3 antibody (green).

Figure 11 shows the induction of IgG⁺ cells following immunization with ovalbumin. Figures 11A and 11B are views showing the BM cells of the recipient mice analyzed by flow cytometry in terms of the presence of human IgG⁺ cells, before and after the immunization with ovalbumin. Figure 11C shows a result of the ELISA and indicates the optical density of human IgM (white column in Figure 11C) and that of human IgG (black column in Figure 11C) in the serum of the immunized recipients (recipient) or non-immunized recipients (control).

Figure 12 shows cytotoxicity mediated by human T cells generated in NOD/SCID/IL2rg-null mice to allogenic target cells. Figure 12A to 12C show the cytotoxicity (% Cytotoxicity) of each of the three CD4⁺ T cell strains in stimulating cells-concentration depending manner (Effector/Target ratio). Figures 12D to 12F show the cytotoxicity of each of the three CD8⁺ T cell strains in stimulating cells-concentration depending manner. The human CD4⁺ T cell strain

was cytotoxic to allogenic LCL (TAK-LCL) used as target cells (Figure 12, none, (◆)). Figure 12 shows the results of an inhibition assay regarding cytotoxicity caused by human T cells with an anti-HLA class I antibody (anti-HLA class I, (■)) or an anti-HLA-DR antibody (anti-HLA-DR, (▲)). KIN-LCL: a negative control (KIN-LCL, (x)).

Replace the paragraph at page 22, lines 20 – 23 with the following:

Human cells were identified as green signals (human X chromosomes) (Figure 4a). Several spleen cells derived from the recipient mice were stained with mouse anti-human CD3, and such cells became red (Figure 4c). Figure ~~[[4d]]~~ 4b is a view obtained by overlaying panel a on ~~panel b~~ panel c. The blue-stained portion represents a nucleus.